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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,043	01/09/2008	Volker Sandig	22112.0002U1	5415

23859 7590 03/08/2011

Ballard Spahr LLP
SUITE 1000
999 PEACHTREE STREET
ATLANTA, GA 30309-3915

EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
03/08/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,043	SANDIG ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12* is/are pending in the application.

4a) Of the above claim(s) *8-10 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed January 12, 2011. Applicants' response to the restriction requirement of July 27, 2010 has been entered. Currently, claims 1-10 and 12 are pending in the application. Claims 1, 3-5, 6, 8-10 and 12 have been amended, and claims 11 and 13 have been cancelled by Applicants' amendment file on filed January 12, 2011.

Election/Restrictions

Applicants' election with traverse of Group I directed to an avian cell line, i.e. claims 1-7 in Applicants' response filed on January 12, 2011 is acknowledged. Additionally, Applicants' election with traverse of the following species is acknowledged:

1) a viral gene for the combination of cellular genes to immortalize an avian cell line by non-viral transfection as recited in claim 1,

2) a first viral gene that is an adenovirus E1A gene from mastadenoviruses as recited in claim 3 (iv) and the second viral gene encoding for an adenovirus E1B55K protein of all groups as recited in claim 3 (iv) ,

3) a cell line derived from duck as recited in claim 3 (i) ,

4) cells of the retina as the cells subjected to immortalization as recited in claim 3(ii),

5) the E1A gene according to the sequence complementary to bp 4230 to 3113 of SEQ ID NO:9, and the E1B gene according to the sequence complementary to bp 2345 to 550 of SEQ ID NO:9.

Response to Applicants' arguments

At pages 6-9 of the remarks filed on 01-12-2011, Applicants essentially argue that inventions listed as Groups I-IV have special technical features because : 1) the art cited by Kim

et al., has been misinterpreted, 2) Kim merely discloses the results o testing the expression of p53 and E2F-1 levels of immortalized cells compared to primary cultured cells (Kim et al., p.2672, lines 2-4; page 2680 under the heading Methods and Materials), 3) there is not suggestion in Kim et al., of making an immortalized cell line by particular steps, 4) Applicants' current claims recite an avian cell line made by insertion of particular genes which may have effect on p53 and E2F-1 and methods of making such a cell line, and 5) according to the Preliminary Report on Patentability, no lack of unity of invention was found for the claims. The above arguments have been fully considered but deemed unpersuasive.

Regarding 1), 3) and 4), with respect to claims 1-6 directed to an avian cell line, they are determined to be a product-by-process claims. Note that generic claim 1 which is comprised in Groups I-IV does not place any specific limitation in relation to the avian cell line comprising a combination of viral and/or cellular genes. Thus the step of " at least one first gene affecting functions of the retinoblastoma protein" and "at least one second gene affecting the p53 protein" implying a step of "affecting " that is explicitly missing from claim 1. The recitation of a process limitation in claim 1 is not viewed as positively limiting the claimed product absent a showing that the process of making imparts a novel or unexpected property to the claimed avian cell line product, as it is assumed that equivalent immortalized avian cell line products are obtainable by various routes. Thud, the recitation "immortalized by" is not considered to limit the avian cell line because the avian cell line may be obtained by other non-viral transfection means. The burden is placed upon the applicants to establish a patentable distinction between the claimed and referenced products. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The

patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP §2113.Accordingly, the method of transfection of the avian cell line, i.e. transfection with a combination of viral and/or cellular genes are not afforded patentable weight, as it is assumed that equivalent avian cell lines products may be obtainable by different methods.

Regarding 2), at page 2677, col. 2, second full paragraph Kim et al., suggests avian cell lines wherein functional studies involving the downregulation of p53 by expression of antisense p53 mRNA and upregulation of E2F-1 by introduction of exogenous E2F-1 could help determine the direct relationship between genetic alterations of p53 and E2F-1 and cellular immortalization, falling within the scope of claim 1. It is noted that case law states that anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure. In re Donohue, 766 F.2d 531, 533 [226 USPQ 619] (Fed. Cir. 1985). A reference may enable one of skill in the art to make and use a compound even if the author or inventor did not actually make or reduce to practice that subject matter. Bristol-Myers, 246 F.3d at 1379; see also In re Donohue, 766 F.2d at 533.

Regarding 5), the question of unity of invention raised by the International Searching Authority has been considered by the examiner and found no persuasive under the meaning of US patent laws.

Accordingly, claims 8, 9, 10 and 12 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being

no allowable generic or linking claim. The requirement for restriction between Groups I-IV is maintained for reasons of record and the foregoing commentary, and hereby made FINAL.

In relation to the rejoining of elected Groups I, drawn to a product , and Groups II-IV, drawn to the process of making and using the product, it is noted that the MPEP 1893.03(d) states: If an examiner (1) determines that the claims lack unity of invention and (2) requires election of a single invention, when all of the claims drawn to the elected invention are allowable (i.e., meet the requirements of 35 U.S.C. 101, 102, 103 and 112), the nonelected invention(s) should be considered for rejoinder. Any nonelected product claim that requires all the limitations of an allowable product claim, and any nonelected process claim that requires all the limitations of an allowable process claim, should be rejoined. See MPEP § 821.04 and § 821.04(a). Any nonelected processes of making and/or using an allowable product should be considered for rejoinder following the practice set forth in MPEP § 821.04(b).

Applicant is reminded of the right to petition under 37 CFR 1.144, if applicant disagrees with the requirements for restriction filed on July 27, 2010. Note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Therefore, claims 1-7 are currently under examination to which the following grounds of rejection are applicable. The claims are examined to the extent that they read on the elected species.

Claim objection

Claims 1 and 3 are objected to because of the following informalities: abbreviations such as E2F, E1A and IB; e.g., the early region 1A (E1A) and IB (E1B) genes should be spelled out at the first encounter in the claims. Appropriate correction is required.

Claim 3 (ii) is objected to because the word "brain" is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the term "and/or" in line 2. It is unclear what the metes and bounds of this term, as "and" could be interpreted to include only viral genes, or all of the genes, or, "or" would imply that the gene types are in the alternative. As such, the metes and bounds of the claims cannot be determined.

Claim 3 (i) and 4 (i) are vague and indefinite in its recitation of the term "derived from" in that the metes and bounds of the term "derived from" are unclear. It is unclear the nature and number of steps required to obtain a "derivative" of a duck cell line (Claim 3 (i)) or a derivative E1A and E1B region from adenovirus 5 (Claim 4 (i)).The term implies a number of different steps that may or may not result in a change in the functional characteristics of a cell line or gene region from the source that it is "derived from". It would be remedial to amend the claim

language to use the term "obtained from", which implies a more direct method of acquiring the duck cell line or .

Claim 3 (ii), and claim 4 (i) and (ii) use parentheses to comments on or qualify part of the sentences. It is unclear whether the limitations in parentheses are meant to be limitations in the claims or whether they are only suggestions/examples. As such, the metes and bounds of the claims cannot be determined.

Claim 4 recites the term “or” in line 7, and the term “and” on line 14. Markush groups using the conjunction “or” and “and” is confusing. Similarly, claim 4 should be amended to recite the group using proper format in this case --selected from at least one of--. Additionally,

for proper claim construction, step (iii) should be amended to recite –combinations of nucleic acid encoding E1A, E1B with GAM-1 and Orf22 as defined in (i) and (ii) above--. As such, the metes and bounds of the claims cannot be determined.

Likewise, claim 3(i), (ii), (iii) and (iv), and claim 5 (i) should be amended to recite the Markush group using proper format in this case --selected from at least one of--. As such, the metes and bounds of the claims cannot be determined.

Claims 2 and 6 are also included in the rejection as they directly depend on claim 1 and they fail to address or clarify the basis of the rejection as discussed in detail for the independent claims.

Claim Rejections - 35 USC § 112-Deposit Requirement

To the extent that claim 7 is depending on claim 1 is drawn to the cell line 12A07-A10 (DSM-ACC2695), the following rejection applies.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification lacks complete deposit information for the deposit of cell line 12A07-A10; DSM ACC2695, deposited on Oct. 20, 2004. Because it is not clear that the properties of this strain are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the best mode disclosed by the specification requires the use of this specific strain, a suitable deposit for patent purposes is required.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of the deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of the deposit and the complete name and full street address of the depository is required.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR §1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

© the deposits will be maintained in a public depository for a period of at least thirty years from the date of the deposit or for the enforceable life of the patent or for a period of five

years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become non-viable or non-replicable.

In addition, a deposit of the biological material that is capable of self-replication either directly or indirectly must be viable at the time of the deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological material not made under the Budapest Treaty must be filed in the application and must contain:

1)The name and address of the depository;
2)The name and address of the depositor;
3)The date of deposit;
4)The identity of the deposit and the accession number given by the depository;
5)The date of the viability test;
6)The procedures used to obtain a sample if the test is not done by the depository; and
7)A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the cell line described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR §1.801-1.809 for further information concerning deposit practice.

It is noted that Applicant has deposited the biological materials (p. 25 of the specification), but there is no indication in the specification as to public availability. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials have been deposited under the Budapest Treaty and that the biological materials will be irrevocably and without restriction or condition released to the public upon an issuance of patent, would satisfy the deposit requirement made herein. If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may provide an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer.

Claim Rejections - 35 USC § 102

Claim 1 is directed to a product by process claim comprising an immortalized avian cell line.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Kim et al. (1995, Oncogene 20: 2671-2682, of record).

Kim et al., discloses a number of non-virally and non-chemically immortalized chicken cell lines characterized by diminished steady-state expression of p53 mRNA with dramatically elevated E2F-1 mRNA levels (abstract). Kim et al., at page 2677, second full paragraph, suggests functional studies involving the downregulation of p53 by expression of antisense p53 mRNA (e.g. reading on at least one second gene affecting the p53 protein) and upregulation of E2F-1 by introduction of exogenous E2F-1 (e.g. reading on at least one first gene affecting the function of the retinoblastoma (Rb) protein by mediating disruption of complexes between Rb protein and E2F transcription factors). Note that Kim et al., describes deregulation of E2F-1 through increased transcription (i.e., regulation of E2F-1 activity is Rb dependent) (page 2677, col. 2).

Therefore the an avian cell line immortalized by non-viral transfection with viral or cellular genes as claimed is necessarily and inherently anticipated by the immortalized chicken embryo fibroblasts of Kim, absent any factual evidence to the contrary, because the structural limitations of the immortalized avian cell line are the same.

Thus by teaching all the claims limitations, Kim et al., anticipates the instant invention.

Claim Rejections - 35 USC § 103

To the extent that the instant claims are interpreted as an avian cell line comprising avian cells obtained from duck which are immortalized by co-transfection of two plasmids, the first comprising sequences encoding the adenovirus sequence for E1A operably linked to an expression control sequence and a second encoding the adenovirus sequence for E1B operably linked under control of a second expression control sequence or 2) transfection of the host avian cells with a single plasmid comprising the first and the second sequences operably linked to an expression control sequence , the following rejection applies.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bouquet et al., (U.S. Patent 6,255,108, Date of patent July 3, 2001) in view of Kim et al. (1995, Oncogene 20: 2671-2682, of record), and further in view of Pau et al., (U.S. Patent 7,192,759, Date of filing November 26, 1999; see Score search results for Application 10/578,043) as evidenced by Bagchi et al., (Cell 1991, pp. 1063-1072) and Renee et al., (1992, Nature pp. 82 – 85) .

Bouquet et al., discloses methods and compositions for producing immortal avian cells lines from primary duck embryo cells such as fibroblasts or epithelial cells for the production of substances of interest (e.g., molecules or viruses for creating diagnostic reagents or vaccines) comprising introducing into host cells a vector which does not exhibit any oncogenic character but which is able to integrate, into these cells, a gene which is selected for its capacity to induce immortalization. Specifically, fibroblasts derived from duck embryos were transfected with a vector expressing the viral oncoprotein SV40 virus early region (encodes the T and t antigens) which integrated into their nucleus and immortalized fibroblasts to generate immortalized TDF-2A cells (col. 5, lines 23-27; col. 6, lines 1-21). Additionally, a vector expressing the bcl-2 gene under the control of the CMV (human cytomegalovirus) promoter was transfected into the

immortalized TDF-2A cells to generate the duck fibroblast line TDF-2A bcl-2 in which apoptosis was deferred as related to control cells at confluency (col. 7, lines 14-32). Though Bouquet et al., does not specifically teach overcoming G1 checkpoint control by SV40 virus early region and preventing induction of growth arrest and apoptosis in culture conditions by down regulation of p53, any prevention in induction of growth arrest and apoptosis is implicitly mediated by p53 in the immortalized, proliferating avian cell line, absent evidence to the contrary (Current claims 1 and 2, in part, claim 3 (i) (ii) in part (iii); claims 5 and 6) .

Bouquet et al., does not particularly teach an immortalizing viral oncoprotein mediating disruption of complexes between avian retinoblastoma protein (Rb, a tumor suppressor protein) and E2F transcription factors.

However, at the time the invention was made, Kim et al., suggests a number of non-virally and non-chemically immortalized chicken cell lines generated by simple transfection of a vector. Kim et al., teaches that functional inactivation of the p53 and Rb regulatory pathways are known to be common events for cellular immortalization (abstract). Kim et al., demonstrates diminished steady-state expression of p53 mRNA while dramatically elevated E2F-1 mRNA levels in immortalized chicken embryo fibroblast (CEF) cells. Moreover, Kim discloses that the activated E2F-1 transcription factor has the ability to induce the expression of several genes involved in cell cycle regulation and DNA synthesis (e.g., cyclin A and cyclin E). Further, the transcriptional activity of E2F-1 can be either stimulated or suppressed depending on its association with Rb (i.e., regulation of E2F-1 activity is Rb dependent). Kim et al., discloses that "in immortal CEF cells, E2F-1 mRNA was continuously up-regulated in all different phases of the cell cycle in immortal CEF cells (and even in serum deprived culture conditions), whereas

the fluctuation in E2F-1 mRNA levels occurred in each cell division in normal cells (data not shown)" which indicates deregulation of E2F-1 through increased transcription. As "The differential expression of both p53 and E2F-1 genes seem to be a common event in immortal CEF cells and could be an early event in the process of cellular immortalization", Kim et al., suggest functional studies involving the downregulation of p53 by expression of antisense p53 mRNA and upregulation of E2F-1 by introduction of exogenous E2F-1 could help determine the direct relationship between genetic alterations of p53 and E2F-1 and cellular immortalization (p. 2677, col. 2) (Current claims 1 and 2, in part).

The combined disclosure of Bouquet et al., and Kim et al., fails to specifically teach an adenovirus E1A gene comprising the sequence complementary to bp 4230 to 3113 of SEQ ID NO:9 which mediates disruption of Rb proteins and E2F transcription factor, and further, an adenovirus gene encoding E1B comprising the sequence complementary to bp 2345 to 550 preventing apoptosis by p53 .

However, at the time the invention was made, immortalization of embryonic retina cells by a gene product of the E1 gene comprising transfection with a plasmid that contained the Ad serotype 5 (Ad5) E1A- and E1B-coding sequences (i.e. Ad5 nucleotides 459 3510 SEQ ID NO:1) under the control of a promoter was known in the art as evidenced by the teachings of Pau et al., (col. 4, lines 26-34, claim 4: see score search results for SEQ ID NO:9 bp 4230-3113 and bp 2345-550). Furthermore, it was known in the art at the time the invention was made that the adenoviral E1A disrupts RB/E2F complexes (Bagchi et al., 1991, Cell, pp. 1063-1072) and the E1B region of the adenoviral genome encodes a 55-kD protein (E1B 55K) that binds and

inactivates p53 contributing to transformation of primary cells (Renee et al., 1992, Nature pp. 82 – 85) (Current claim 4).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made in an attempt to establish the direct relationship between genetic alterations of p53 inducing apoptosis and E2F-1 in cellular immortalization of avian cell lines, to substitute the vector expressing the viral oncoprotein SV40 virus early region of Bouquet et al., for another viral oncogene mediating the disruption of complexes of E2F and Rb as taught by Kim, particularly because Kim et al., discloses deregulation of E2F from its association with Rb to immortalize avian cell lines. Likewise, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to substitute the antiapoptotic gene bcl-2 of Bouquet et al., for a gene affecting the p53 protein or a family member downregulating p53 by expression, particularly because Kim et al., suggest that inactivation of both p53 and E2F/pRB complexes seems to be a common event in immortal CEF cells and could be an early event in the process of cellular immortalization. Furthermore, one of skill in the art would have recognized that the results of the combination of Ad5 oncogenes E1A and E1B encoded by a gene region comprising bp 4230-3113 and bp 2345-550 of SEQ ID NO:9 would have yielded the predictable results of inducing cell proliferation by disrupting Rb/E2F complexes and inactivating p53, as these pathways where known in the art to be necessary for neoplastic transformation. Moreover, selection of retina cells as primary avian cells for immortalization would be a matter of design of choice. The manipulation of previously identified DNA fragments and cell transformation systems comprising simple transfection of a vector is within the ordinary level of skill in the art of molecular biology. Thus, all of the elements of the claims were known

to one of ordinary skill in the art at the time the invention was made and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of invention.

Thus, in view of the foregoing, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

The cited prior art meets the criteria set forth in both Graham and KSR, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is prima facie obvious.

Conclusion

Claims 1-7 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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